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# Carbamazepine Extended-Release Capsules Use in Bipolar Disorder: Efficacy and Safety in Adult Patients

**LAWRENCE D. GINSBERG, MD**
Red Oak Psychiatry Associates, Houston, TX, USA

***Background.*** *Safety, tolerability, and efficacy of carbamazepine (CBZ) have been demonstrated in numerous studies over the last three decades. Until recently, CBZ studies largely involved immediate-release formulations, while long-term studies have been few in number. The recent development of beaded CBZ extended-release capsules (CBZ-ERC) (Shire, Wayne, PA, USA) provides a new formulation with potential advantages in safety, tolerability, and efficacy over earlier formulations.*
***Methods.*** *The present study assesses these parameters in patients of various bipolar subtypes (mixed/manic, bipolar I depression, and bipolar II), in a single-site private practice setting. Data were obtained from the charts of 300 patients ≥ 18 years old who met* DSM-IV *criteria for bipolar disorder. Clinical response to CBZ-ERC therapy was defined as a score of ≤ 3 on the Clinical Global Impression–Improvement (CGI-I) scale, while relapse was defined as a change in CGI-I to ≥ 4 in those subjects who had previously achieved clinical response.*
***Results.*** *Clinical response occurred in 73% of patients, leading to a mean CGI-I score of 2.5 (SD = 1.2). Relapse was seen in 33% of responders. Most common adverse events were somnolence, dizziness, and nausea. A high level of treatment response and a low relapse rate were observed in long-term treatment with CBZ-ERC in adults with bipolar disorder. The limited number and nature of the adverse events observed during the course of this study provide evidence of the safety and tolerability of CBZ-ERC.*
***Conclusions.*** *Carbamazepine extended-release capsules appear safe and efficacious for the treatment of bipolar disorder. Controlled studies are warranted to further establish the safety, tolerability, and efficacy of CBZ-ERC for treatment of adult bipolar patients.*

**Keywords** Adult, Bipolar disorder, Carbamazepine

## *INTRODUCTION*

There is an increasing number of pharmacologic options for the treatment of bipolar disorder, perhaps the most prominent of which are lithium, valproate, carbamazepine (CBZ), and the atypical antipsychotic olanzapine (1–3), though other agents such as aripiprazole (4), ziprasidone (5), risperidone (6), and quetiapine (7) are approved for the indication. All agents possess certain benefits and drawbacks in terms of safety, tolerability, and efficacy. Lithium is associated with efficacy in bipolar I, although it appears less successful in treating mixed mania and concurrent substance abuse, and is prone to causing weight gain (8–11). Valproate has also proven effective in treating acute mania and appears to be efficacious in rapid cycling (12). Its disadvantages include a propensity for weight gain and hair loss, a sedating profile, and an association with polycystic ovarian syndrome (13–15). Olanzapine, a more recent agent, has been shown to be effective in treating mania; however its side effect profile includes a high propensity for weight gain, as well as strong associations with dyslipidemia, diabetes, and potentially life-threatening diabetic ketoacidosis (12,16–19). Carbamazepine has both a sedating profile and the capacity for drug-drug interactions, but it has been particularly successful in treating "nonclassical" bipolar disorder, including bipolar depression, bipolar II, and bipolar not otherwise specified (NOS) (8,10,14). Studies suggest that it is equivalent to lithium in efficacy and tolerability in treating acute mania and is associated with a low risk of weight gain (3,20).

Carbamazepine has been applied to the treatment of bipolar disorder for approximately 30 years (21). It is tricyclic in structure

Address correspondence to Lawrence D. Ginsberg, MD, Red Oak Psychiatry Associates, 17115 Red Oak Drive, Suite 109, Houston, TX 77090. E-mail: larrydg@earthlink.net

and alters neurotransmission related to the pathophysiology of mood disorders (22). Among these neurotransmitter changes, CBZ possesses both GABAergic and antiglutamatergic effects (23). In addition to its sedating effect, it also has mild antidepressant properties (24). Carbamazepine is available in numerous formulations, including immediate release, slow release, suspensions, syrups, and chewable tablets. More recently, beaded CBZ extended-release (CBZ-ERC) (Shire, Wayne, PA, USA) has been developed that may provide some of the advantages associated with extended-release formulations, including less variability in serum levels, lower incidence of adverse events, improved dosing convenience, and therefore greater medication adherence (25,26).

Recent studies of the CBZ-ERC formulation in bipolar treatment—two 3-week studies and one 6-month study—demonstrated efficacy, safety, and tolerability for bipolar patients with mixed and manic episodes (20,23,27). Although these studies demonstrated that CBZ-ERC can be used to treat acute manic/mixed patients, little is known about its role as a treatment option for bipolar I depressed or bipolar II patients. The present study seeks to increase knowledge about this newer CBZ formulation by examining the long-term tolerability and efficacy of CBZ-ERC in an adult population being treated for bipolar disorder (including acute mixed/mania, bipolar II, and bipolar I depression subgroups) in a single private practice setting. Tolerability was determined by monitoring and recording all patient adverse events. Efficacy was determined by treatment response and relapse rates. Mixed/manic patients were compared with bipolar II and bipolar I depression patients to determine if CBZ-ERC had similar safety and response profiles.

## *METHODS*

### *Study Design and Subjects*

A retrospective review was conducted in a single-site private practice setting (Red Oak Psychiatry Associates, Houston, TX) of charts of 300 outpatients treated between October 1998 and November 2003 who met DSM-IV criteria for bipolar disorder. Study subjects were adults ≥ 18 years old who had been treated for bipolar disorder with CBZ-ERC. Data on the study subjects were drawn exclusively from chart review. Patients were taking other drugs as well.

### *Study Assessments and Data Analysis*

Data obtained from patients' charts included diagnosis of both primary (i.e., bipolar) and comorbid conditions, dose of CBZ-ERC, and concomitant medications taken at initiation and discontinuation of therapy. Primary diagnosis included bipolar subtype—bipolar I, bipolar II, or bipolar NOS—and most recent episode (manic, mixed, depressed, etc.).

Demographic data were extracted from patients' charts, as well as information regarding adverse events, suicide attempts, hospitalizations, white blood cell count (WBC), and assessment of both illness severity and improvement using two National Institute of Mental Health Clinical Global Impression (CGI) scales, the CGI-Severity (CGI-S) scale and the CGI-Improvement (CGI-I) scale (28). The CGI-S scale ranges from a score of 1 (no mental illness) to 7 (severe mental illness), and the CGI-I scale ranges from a score of 1 (very much improved) to 7 (very much worse). Severity of illness (CGI-S) was established at initiation of CBZ-ERC therapy. Global improvement (CGI-I) was measured at subsequent office visits in order to evaluate response to CBZ-ERC therapy. Clinical response to CBZ-ERC therapy was defined as a score of ≤ 3 on the CGI-I scale. Relapse was defined as a change in CGI-I to ≥ 4 in those subjects who had previously achieved clinical response with CBZ-ERC therapy.

Subanalysis of chart data was conducted to establish the effect of CBZ-ERC therapy on specific bipolar subpopulations. A subpopulation group, consisting of both pure manic and mixed subjects, was compared with bipolar I depression subjects and bipolar II subjects, respectively. Analysis of clinical and demographic comparisons were performed with one-way analysis of variance or contingency tables (chi-square test).

## *RESULTS*

### *Patient Characteristics*

The baseline characteristics of the patients included in this chart review are presented in Table 1. Of the 300 subjects included in this retrospective chart review, 70.6% were female; ages ranged from 18 to 70 years, with a mean age of 35.1 years (SD = 11.3). At initiation of therapy, 94 patients (31.3%) received CBZ-ERC monotherapy; the remainder received CBZ-ERC with ≥ 1 concomitant medication. The average dose of CBZ-ERC at the patient's lowest CGI-I visit was 581.3 mg/d (SD = 212.8) (Table 1).

**Table 1** Baseline Patient Demographics at Initiation of CBZ-ERC Therapy

| Characteristic | Value |
|---|---|
| Participant number | 300 |
| Gender (% female) | 70.6 |
| Mean age (years) (SD) | 35.1 (11.3) |
| Age range (years) | 18–70 |
| CBZ-ERC monotherapy at start of study (%) | 31.3 |
| CGI-S (% of total) | |
| Moderately ill (CGI-S = 4) | 16.0 |
| Markedly ill (CGI-S = 5) | 52.0 |
| Severely ill (CGI-S = 6) | 25.0 |
| Extremely ill (CGI-S = 7) | 7.0 |

CBZ-ERC = carbamazepine extended-release capsules; CGI-S = Clinical Global Impression–Severity.

**Table 2** Bipolar Diagnosis by Subtype

| Bipolar subtype | Percentage of patients (%) |
|---|---|
| *Bipolar I (n = 204)* | *68.0* |
| Depressed | 21.0 |
| Depressed, RC, UC | 1.3 |
| Manic | 10.0 |
| Manic, RC | 0.3 |
| Mixed | 31.0 |
| Mixed, RC | 2.0 |
| Mixed, Psychotic | 2.3 |
| *Bipolar II (n = 45)* | *15.0* |
| II | 14.3 |
| II, RC | 0.7 |
| *Bipolar NOS (n = 51)* | *17.0* |
| NOS | 16.7 |
| NOS, UC | 0.3 |

RC = rapid cycling; UC = ultradian cycling; NOS = not otherwise specified.

**Table 3** Comorbid Conditions of the Patients in This Study

| Comorbid condition | Percentage of total number of patients (n) |
|---|---|
| *All comorbid conditions* | *68.7 (206)* |
| Panic disorder | 16.7 (50) |
| Substance abuse | 14.3 (43) |
| Generalized anxiety disorder | 13.3 (40) |
| Attention-deficit/hyperactivity disorder | 9.7 (29) |
| Alcohol abuse | 8.0 (24) |
| Post-traumatic stress disorder | 4.0 (12) |
| Obsessive-compulsive disorder | 2.7 (8) |

More than two thirds of study subjects (68%) received a diagnosis of bipolar I, while the remaining patients received either a bipolar II or bipolar NOS diagnosis. Bipolar disorder subtype and most recent episodes are listed in Table 2. A majority of patients were also diagnosed with ≥ 1 comorbid Axis I condition as shown in Table 3. Panic disorder was most common, occurring in 50 patients (16.7%). Forty-three patients (14.3%) were substance abusers, and 24 (8%) abused alcohol. Generalized anxiety disorder was prevalent in 40 patients (13.3%), while 29 patients (9.7%) received a diagnosis of attention-deficit/hyperactivity disorder. Post-traumatic stress disorder was found in 12 subjects (4%), and 8 patients (2.7%) experienced obsessive-compulsive disorder. Scores on the CGI-S at treatment initiation indicated that 7% of the study population was extremely ill, 25% severely ill, 52% markedly ill, and 16% moderately ill (Table 1).

### *Treatment Response and Relapse*

The mean CGI-I score for the study population was 2.5 (SD = 1.2). Clinical response to CBZ-ERC therapy (i.e., CGI-I ≤ 3) occurred in 73% of patients. Among these clinical responders, relapse (i.e., subsequent change in CGI-I to ≥ 4) occurred in one third of patients (33%) during the course of the study.

### *Concomitant Medications*

More than two thirds of patients (68.7%) received ≥ 1 concomitant medication at initiation of CBZ-ERC therapy. The most commonly used of these medications were clonazepam (11.3%), escitalopram oxalate (10.3%), and venlafaxine in both immediate-release and extended-release formulations (10%).

### *Treatment-Emergent Adverse Events and Suicidal Behavior*

The frequency of treatment-emergent adverse events is reported in Table 4. Somnolence was the most frequently recorded adverse event, as is common in treatment with CBZ-ERC, occurring in 11% of patients, followed by dizziness (7.7%), nausea (7.7%), and rash (5.3%; severity of rash was not recorded). Headaches were noted in 4% of patients, while asthenia and increased appetite were each seen in 2.7% of participants. While full reporting of WBC data was not available, it was established that a total of 3 patients discontinued treatment due to low WBC count. Attempted suicide was documented in 6 patients during CBZ-ERC treatment.

### *Comparisons by Bipolar Subtype*

Although CBZ is long established in treating mixed and manic subtypes of bipolar I disorder, it is not well studied among patients with bipolar I depression or in bipolar II disorder. Therefore, two separate subanalyses were undertaken to compare the response of pure manic and mixed patients with the respective response rates of bipolar I depression and bipolar II patients. The manic/mixed group (n = 137) was compared with the bipolar I depression patient group (n = 67). No significant differences were found between the groups with respect to gender, mean age, baseline CGI-S, CGI-I, response, relapse, or adverse events. The demographics of the cohorts, as well as the efficacy and safety of CBZ-ERC, were not significantly different

**Table 4** CBZ-ERC Treatment-Emergent Adverse Events

| Adverse event[a] | Percentage |
|---|---|
| Somnolence | 11.0 (33) |
| Dizziness | 7.7 (23) |
| Nausea | 7.7 (23) |
| Rash | 5.3 (16) |
| Headaches | 4.0 (12) |
| Asthenia | 2.7 (8) |

CBZ-ERC = carbamazepine extended-release capsules.
[a]Adverse events occurring in greater than 2% of the population are listed.

between manic/mixed and bipolar I depression patients in this study.

The bipolar II group (n = 45), like the bipolar depression group, was not significantly different from the manic/mixed group in terms of demographics, response, and relapse. Differences in the mean CGI-S scores (5.3 [SD = 0.8] for the manic/mixed group compared to 5.0 [SD = 0.7] for bipolar II patients) were not significant ($P = 0.12$). CGI-I scores were also not significantly different between the two groups ($P = 0.6$), with mixed/manic patients having a mean CGI-I score of 2.4 (SD = 1.2) compared to bipolar II patients with a mean score of 2.5 (SD = 1.3). Treatment response was 75.2% versus 68.9% ($P = 0.52$) for the manic/mixed and bipolar II groups, respectively. There were no significant differences in either relapse rates between the two populations, or in adverse events (except for dizziness, which occurred in 11.1% of bipolar II patients compared with 2.2% of manic/mixed patients) ($P = 0.03$).

## *DISCUSSION*

While CBZ has been used for three decades in bipolar disorder, the introduction of a beaded, extended-release formulation provides certain potential advantages over earlier formulations. Extended-release formulations promote more stable serum levels than immediate-release formulations. Studies of extended-release CBZ in epilepsy patients have shown less variability in absorption compared to immediate-release CBZ, and have allowed for a subsequent reduction in central nervous system side effects such as ataxia, vertigo, discoordination, sedation, diplopia, and confusion (26,29). Quality of life also improved in patients taking extended-release CBZ compared to conventional formulations (30,31). Extended-release medications provide greater convenience, and in the case of CBZ-ERC, twice-daily dosing may be compared with 3- or 4-times-daily dosing for immediate-release CBZ. An increase in dosing convenience is associated with improved medication adherence. The capsule formulation of CBZ-ERC is likely to promote even better adherence since it can be sprinkled on soft foods or taken with no food at all, unlike extended-release tablets or immediate-release CBZ formulations (32).

The present retrospective review seeks to help fill a gap of long-term controlled clinical studies examining CBZ-ERC in bipolar disorder; the size of the study population (300 patients) makes it the largest CBZ-ERC study for bipolar patients to date. It deals with a diverse bipolar population, about two thirds of whom had received a bipolar I diagnosis and one third either a bipolar II or bipolar NOS diagnosis. The diversity of the study population is of some interest in light of evidence that CBZ is particularly well suited to nonclassical bipolar patients (i.e., bipolar II, bipolar NOS, mixed states, and substance abuse) (8). The results showed a high level of CBZ-ERC treatment response, with 73% of patients responding to therapy, based on CGI-I scores. A low treatment relapse rate of 33% was further seen among treatment responders.

Recent studies of CBZ-ERC in bipolar patients with manic or mixed episodes have demonstrated efficacy and a low relapse rate, as well as safety and tolerability (20,27). A 3-week, double-blind, placebo-controlled study by Weisler and colleagues of 204 patients with manic or mixed episodes found significantly greater improvements in the CBZ-ERC group for manic symptoms as measured by CGI-I, CGI-S, and the Young Mania Rating Scale (YMRS) compared with placebo (27). Mixed bipolar patients taking CBZ-ERC were improved significantly compared to placebo patients, based on the Hamilton Rating Scale for Depression (HAM-D).

A 6-month, multicenter, open-label study, that was a continuation of the Weisler study found that improvements in CGI-I, YMRS, and HAM-D were maintained over the 6 months of treatment (20). Placebo group participants from the short-term studies who were given CBZ-ERC in the 6-month study also showed significant improvements. Patients using CBZ-ERC in the 6-month study experienced a low relapse rate of 14.3%, which may be compared to relapse rates of 29% for lithium and 74% for placebo according to a meta-analysis of 19 blinded, randomized, controlled trials by Davis and associates (33).

Previous studies of conventional CBZ formulations have shown a general equivalence in efficacy compared with lithium, although there does exist some variability in the results. A meta-analysis by Dardennes and colleagues looked at four randomized, double-blind controlled studies comparing CBZ and lithium in maintenance therapy. Three of the four studies found the medications equally effective, and the fourth favored lithium (34). A literature review by McElroy and Keck summarized studies confirming the equivalence of CBZ and lithium in efficacy and tolerability (3). A long-term randomized study by Greil and associates found no significant difference in recurrence between lithium and CBZ, although when concomitant psychotropic medications were included, the data favored lithium (11). A 3-year, double-blind crossover study, which included 1 year of lithium therapy, 1 year of carbamazepine therapy, and 1 year of combination therapy, found lithium to be superior in mania, CBZ to be superior in bipolar depression, and combination therapy to be generally superior to both monotherapies (10).

The Multicenter Study of Long-term Treatment of Affective and Schizoaffective Psychosis (MAP), a randomized, multicenter clinical trial of 171 bipolar patients over a period of 2.5 years, is of particular interest because of the extent of its data analysis (8). This analysis includes division by bipolar subtype, an examination of the effect of episode sequence on efficacy, and patient satisfaction. Overall, bipolar I patients experienced better efficacy with lithium, while bipolar II and bipolar NOS patients did better with CBZ. Episode sequence was largely not significant with regard to efficacy. Patient satisfaction favored CBZ.

In the present study, adverse events occurred at a relatively low rate, which may be at least in part a consequence of the reduced variability of serum levels inherent in an extended-release formulation. The low incidence of headache, dizziness, and nausea—4%, 7.7%, and 7.7%, respectively—is particularly

notable. When broken down by subtype, dizziness in mixed and manic patients was exceptionally low (2.2%), though somewhat higher among bipolar II patients (11.1%). Overall, these data support the results from previous studies demonstrating safety and tolerability in CBZ-ERC therapy (20,27).

The limitations of this study are typical of retrospective chart reviews. These shortcomings include incomplete data on adverse events; for example, weight gain, although generally low in CBZ (20), was not reported. The high numbers of patients with comorbid conditions and the many patients taking (and changing) concomitant medications make it difficult to draw definite conclusions regarding the cause of adverse events. The length of CBZ-ERC treatment could not be reported for the entire study population, since for some patients, treatment was ongoing at the time of chart review. Despite the limitations, a retrospective chart review can provide insight into the tolerability and efficacy of CBZ-ERC therapy in a private practice setting, which is inevitably less controlled than a clinical trial, but more closely mimics the actual treatment environment for the majority of bipolar patients. Nonetheless, continued studies under double-blind, controlled conditions are warranted to further establish the safety, tolerability, and efficacy of CBZ-ERC in the adult population.

## *CONCLUSIONS*

This retrospective chart review supports previous double-blind, placebo-controlled, and open-label studies showing CBZ-ERC treatment to be safe and tolerable for manic/mixed bipolar disorder (27,35). This study also suggests CBZ-ERC is equally effective and safe for individuals diagnosed with bipolar II disorder and bipolar I depression. In conclusion, within the limitations of the study, efficacy, tolerability, and a low relapse rate were observed in adult bipolar patients in a clinical setting.

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